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Apathy: a separate syndrome from depression in dementia? A critical review

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ABSTRACT. Apathy and depression are the most prevalent neuropsychiatric symptoms in Alzheimer's disease and mild cognitive impairment. Despite much research on apathy and depression in dementia, the nosological position of apathy as a separate syndrome from depression remains debated. This literature review provides a critical analysis of the areas of clinical manifestation, symptomatology, assessment, prevalence and neuropathology. Evidence does not provide a clear view of the nosological position of apathy in dementia for symptoms and neuropathology. However, the ambiguity of the evidence may be attributed in large part to a lack of clarity in definition and etiology, clinical criteria and assessment overlap. Given the evidence, it is concluded that the argument in favor of apathy as a separate syndrome from depression in dementia is persuasive. Reaching a consensus on the definition and nosological position of apathy within dementia is vital to provide patients and caregivers with the support they require, increase understanding of risk factors, and enable comparisons across research and practice.

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INTRODUCTION

Apathy and depression are prevalent neuropsychiatric symptoms in Alzheimer's disease (AD) and mild cognitive impairment (MCI) (1). While closely clinically related, demonstrating co-morbidities and key symptom overlap (e.g., loss of interest and motivation, reduced activity or hedonism, and lack of insight) (2, 3), they are also pathophysiologically distinct (4), and several studies indicate two separate syndromes, with differential prevalence rates, neuropsychiatric symptoms and cognitive functions (2, 4-7). The nosological position of apathy as a separate syndrome from depression remains debated (3, 8, 9) despite extensive research. Review and research papers mostly address this issue only briefly, not providing in-depth understanding of how and why apathy and depression differ in dementia. For example, Ishii et al. (7) provided a detailed review on apathy as a common psychiatric syndrome in the elderly, but offered only a subsection on the differentiation analysis, both in support of apathy as a separate syndrome from depression and apathy as a symptom of depression. To our knowledge, only Tagariello et al. (9) provide a literature review on this specific subject. Due to its brevity, it only provides a summary of the main issues and does not provide a comprehensive evaluation. The present paper provides an in-depth analysis, examining research both in support of apathy as a separate syndrome from depression and apathy as a symptom of depression.

APATHY IN DEMENTIA

Apathy is a behavioral and personality change prominently observed in AD, and is generally defined as a loss of motivation, manifested in behaviors of diminished initiation, poor persistence, lack of interest, indifference, low social engagement, blunted emotional response, and lack of insight, not attributable to decreased consciousness levels, cognitive impairment or emotional distress (10, 11). Marin et al. (12-14) originally defined apathy as a lack of motivation (i.e., direction, intensity and persistence of goal-directed behavior) relative to the patient's previous level of functioning or standards of age and culture, as indicated either by subjective accounts or observations by others. While their (13, 14) concept of apathy centers on reduced goal-directed behavior, cognition or emotion (15), modern conceptualizations acknowledge apathy as reflecting a multitude of

Key words: Alzheimer disease, apathy, behavioral and psychological symptoms of dementia, dementia, depression.

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dimensions (16): a disorder of motivation, with cognitive, sensory, motor and affective subtypes (12); a disorder of interest or motivation, including lack of emotion, initiation and enthusiasm (17); a disorder of initiative, manifested in a lack of self-initiated action (affective, behavioral or cognitive) and including 'social apathy' (a disorder of the sense of self and of social awareness) (18); a disorder of motivation, with emotional blunting, lack of initiative and lack of interest (19); a disorder of intellectual curiosity, action initiation, emotion and self-awareness (20); a disorder of voluntary and goal-directed behaviors, with three subtypes of disrupted "signal" processing: emotional-affective, cognitive and auto-activation (15); and a disorder of motivation, with diminished goal-directed behavior and cognition (21). Despite these differing views on the core features of apathy – namely, whether the central feature of apathy is disturbance of motivation (12) or initiative and self-generated voluntary and purposeful behavior (15, 18) – the consensus is that motivation, interest, action, initiation and emotional reactivity are dimensions of apathy, in which the changes in motivation may relate to either internal (self-conducted behavior) or external stimulation, and that the lack of motivation is central to the disorder (16). A correlation has been found between apathy and increased cognitive impairment, as well as lower cognitive test performance (22, 23), higher conversion rates from MCI to AD (24), depression (25, 26), and increased impairment in functional activities (10, 27). Notably, while Robert et al. (28) found no association between apathy and executive dysfunction, recent studies demonstrate apathy to be linked – especially in the early stages of cognitive dysfunction (i.e., MCI) – with executive dysfunction and especially worse performance in verbal memory, naming, set shifting and verbal fluency (29-31).

Apathy is an important indicator of early AD diagnosis, strongly correlated with more impairments of daily living activities than normally associated with cognitive status, increased dependency on caregivers to initiate activities and provide support and management (e.g. initiation of activities for which the patient is actually still capable of performing independently), reduced quality of life, rapid progression of cognitive degeneration and various psychobehavioral disturbances, which all contribute to heightened caregiver distress and burden (5, 10, 11, 27, 32-36). Assessing apathy in AD is complicated, as loss of motivation must be differentiated from loss of ability (11). This is particularly difficult in the cognitively impaired, as apathy is generally defined as a reduction in behavior in comparison to the patient's pre-morbid state (11). Cognitive function decline complicates such an assessment, as patients face increased difficulty in the organization and conduct of complex behaviors, reduced behavior resulting from impaired motivational abilities, reduced task initiation, and increased frustration and confusion with hobbies (11, 13, 37). Although apathy is a behavioral sign of cognitive dysfunction in which impairments negatively affect the initiation, planning, and problem-solving of successful task performance (11, 38-40), Marin and Wilkosz (41) observed apathetic individuals generally to be 'able to initiate and sustain behavior, describe their plans, goals and interests, and react emotionally to significant events and experiences' despite diminished motivation associated with apathy (21, pp. 1088-1089). Apathy must therefore be distinguished from cognitive decline, as the dynamic interaction between apathy and cognitive impairment may result in AD patients demonstrating less interest in regular activities as they lose the ability to engage in cognitively complex behaviors and become less likely to initiate regular activities in which they are unsure of the steps required (11). Consequently, apathetic symptoms must be considered when increased functional impairments and reliance on caregiver initiation become more evident than expected for a given level of cognitive impairment (11).

The need for applicable diagnostic criteria for apathy in dementia was originally addressed by Starkstein et al. (10, 21) and recently revised by Robert et al. (16). Starkstein et al. (10, 21) operationalized the definition of apathy of Marin et al. (12) into applicable diagnostic criteria which require: 1) the presence during most of the day for a minimum of 4 weeks of at least one symptom of diminished goal-directed behavior (e.g., lack of effort and initiative, or energy to perform everyday activities; dependency on prompts from others to structure everyday activities); diminished goal-directed cognition (e.g., lack of interest in learning new things or in new experiences; lack of plans and goals, lack of concern about one's own health, functional status or personal problems) or diminished concomitants of goal-directed behavior (e.g., unchanging or flat affect; lack of emotional responsiveness to positive or negative events and restricted responses to important life events); 2) clinically significant distress or impairments in social, occupational or other important areas of functioning caused by apathetic symptoms; and 3) symptoms are not due to a diminished level of consciousness or direct physiological substance effects (e.g., drug abuse, medication) (10, 21). Thus, diminished motivation, initiative and interest, and emotional blunting are at the core of Starkstein et al.'s definition of apathy (16). These criteria have recently been revised into semi-operationalized criteria by Robert et al. (16) based on the synthesis of current concepts of apathy applicable to both research and practice. The revised criteria follow Starkstein et al. (10, 21) structure, and require: 1) loss of or diminished motivation compared with previous functioning levels, not consistent with age or culture, and reported either by the patient or observers; 2) the presence of

impairments (minimum of one symptom) in at least two of the apathetic dimensions of reduced goal-directed behavior, goal-directed cognitive activity, and emotions in which motivational changes are assessed by responsiveness to either internal (self-conducted behavior) or external stimulation (16); 3) functional impairments attributable to apathy; and 4) the exclusion of symptoms and conditions mimicking apathy (42). Future research is required to assess not only the reliability and validity of these criteria, but also the proposed distinction between changes in motivation relating to internal and external stimulation and the impact which such differentiation may have.

DEPRESSION IN DEMENTIA

Depression in AD is characteristically expressed by the high frequency of motivational disturbances (e.g., fatigue, psychomotor slowing and apathy), symptoms of social isolation, withdrawal, irritability or emotional distress, and vegetative symptoms of diminished interest, psychomotor retardation, fatigue, hypersomnia and lack of insight (2, 13, 43-46). While these vegetative symptoms are also key symptoms of apathy (2, 13, 44), depression differs from apathy according to key clinical dysphoric symptoms of sadness, feelings of guilt, self-criticism, helplessness and hopelessness (44), and concurrent reports in the literature propose dysphoria and loss of interest as the most common symptoms of depression in AD (46, 47). However, these findings may be tautological, due to assessment requirements (46, 47). Notably, depressive AD patients demonstrate significant impairments in quality of life, activities of daily living and executive function, although no differences are observed for attention, language, memory and visuospatial functions compared with patients with no changes in mood (48-53). Depression in AD has far-reaching consequences. For AD patients, depression is associated with increased likelihood of physical aggression, being discharged from an assisted living facility and earlier entry into a nursing home, and higher mortality and suicide; for caregivers, it is associated with higher personal depression and burden (44, 52, 54-60). Risk factors for depression in AD include a family history of mood disorders (affective disorders) in first-degree relatives, prior personal depressive history, female gender, and younger age at AD onset (50, 56, 61-65).

Assessing depression in AD is complicated, as symptoms of psychomotor slowing, emotional lability, crying spells, insomnia, weight loss, inability to verbalize affective states and pessimism are prevalent in both depressed and non-depressed AD patients (44, 66). Standardized diagnostic criteria such as the Diagnostic and Statistical Manual of Mental Disorders (DSM) or the International Classification of Diseases (ICD) (67) have been implemented to assess depression in AD. For example, in the DSM-IV criteria for depression, a principal symptom is loss of interest or pleasure in activities as opposed to depressed mood itself (68). However, in the demented, such a loss of interest or pleasure may reflect more a loss of motivation or ability, rather than a change in affect or depression (5). This symptom overlap (e.g., lack of interest, anxiety, lack of energy, concentration difficulty, agitation or psychomotor retardation, sleep and eating disorders) has not only resulted in blurring between AD and depressive symptomology (46, 47, 60, 67, 69), but also resulted in apathetic individuals meeting the diagnostic criteria for major depression even in the absence of dysphoric symptoms (5, 70, 71).

A further limitation of the use of non-dementia specific assessments is their reliance on ability to report subjective depressive symptoms verbally (e.g., mood changes, loss of interest, hopelessness), a process commonly impaired in AD patients (69). Non-dementia specific diagnostic criteria for depression (e.g., DSM, ICD), developed for use in younger, cognitively unimpaired individuals, lack sensitivity to differentiate accurately between symptoms of cognitive decline and depression, and have decreased validity in AD samples (46, 47, 60, 67, 69, 72). This may be explained by differences in clinical manifestations of late life mood disturbance compared with younger life, and the denial by the depressed elderly of sad mood, who rather report lack of feeling or emotion and acknowledge a loss of interest and pleasure in activities (i.e., the depressive elderly report fewer affective symptoms – known as 'depression without sadness') (46, 47, 60, 67, 69, 72-74).

Pertinently, depression and dementia overlap in the under-reporting of depressive symptoms by dementia sufferers and increased reliance on caregiver and observational reports (44, 75). Due to aphasia, many dementia patients lack the ability to express their distress coherently – a further complication when diagnosing depression in AD (44). In addition, the tendency of depressive AD patients to deny the presence of depressed moods and report instead a lack of feeling or emotion, or loss of interest and pleasure in activities, hampers diagnosis with non-dementia specific assessments of depression in the elderly, with and without cognitive impairment (44). This, and the observed difference in depressive symptoms between the elderly with and without dementia, led Olin et al. (46, 69) to propose depression in AD as an atypical form, in which motivational symptoms and delusions are experienced more frequently than by non-cognitively impaired patients (67, 76, 77).

Such difficulties in assessment led Olin et al. (46, 69) to develop the National Institute of Mental Health Provisional Diagnostic Criteria for Depression of Alzheimer's Disease (NIMH-dAD), based on criteria for major depressive episodes (78), but broadened to include those AD patients who experience 'clinically significant affective disturbances but do not meet the standardized diagnostic

criteria for depression' (67, p. 590). The NIMH-dAD diagnostic criteria have been modified to be independent of verbal expression (i.e., subjective reporting) and not confounded by cognitive AD symptomology, and are aimed at improving understanding of the nosology, etiology and treatment of AD-related depression (46, 69). The NIMH-dAD criteria require 1) the presence of three (or more) symptoms of clinically significant depressed mood (e.g., depressed, sad, hopeless, discouraged, tearful); decreased positive affect or pleasure as a response to social contact and usual activities; social isolation or withdrawal; appetite disruption; sleep disruption; psychomotor changes (e.g., agitation, retardation); irritability; fatigue or loss of energy; feelings of worthlessness, hopelessness, or excessive or inappropriate guilt; or recurrent thoughts of death or suicidal ideation (plan or attempt); 2) that all criteria for Dementia of Alzheimer Type of the DSM-IV-TR are met; 3) that significant distress or disruption to functioning is caused by the symptoms; 4) that symptoms are not exclusive to the course of delirium, nor the direct result of physiological substance effects (e.g., drug abuse, medication), or that the symptoms may be better explained by other conditions (e.g., major depressive disorder, bipolar disorder, bereavement, schizophrenia, schizoaffective disorder, AD psychosis, anxiety disorder, or substance-related disorder) (69).

The NIMH-dAD proposes that AD-related depression has heterogeneous etiology characterized as one of four subtypes: 1) emotional reaction to cognitive deficits in AD (e.g., adjustment disorder with depressed mood), in which the depressive state may be a reaction to the diagnosis of AD and/or associated with the awareness of loss and disability, or a reaction of certain personality types vulnerable to depressive symptomology in response to negative life events; 2) recurrence of early and midlife major and minor depressive disorders is a risk factor for later life dementia, and may share its etiology with early or midlife depression; 3) vascular diseases associated with AD causing depressive symptoms (so-called vascular depression), in which occurrence of subcortical lesions in depressed elderly patients with vascular disease indicate that vascular depression results from 'critical lesions or an accumulation of lesions leading to disruption of frontostriatal pathways or their modulating systems'; 4) the neurodegenerative process of AD causes depressive symptoms (e.g., mood disorder due to general medical condition), with pathophysiological overlap between AD and the depressive syndrome in AD, in which the 'neurodegenerative process may directly contribute to the development of depressive symptoms' (44, pp. 357-358). This set of criteria has been shown to be particularly sensitive, with higher rates of depression reported in both retrospective (27.4%) (67) and prospective (44%) (43) implementations of the NIMH-dAD compared with other sets of criteria (e.g., DSM-IV, CAMDEX and ICD-10). In support of Olin et al.'s (46) proposition, Teng et al. (43) demonstrated that an interview using NIMH-dAD criteria more effectively distinguishes significant depressive symptoms in AD patients. Notably, while the symptoms of psychomotor changes, fatigue and guilt/worthlessness were found to predict depression, the newly included symptoms of social isolation/withdrawal and irritability were found not to do so (43). This led the authors to conclude that these symptoms may be more specific for depressive manifestation in AD rather than influence the rate of depression (43). Nonetheless, the NIMH-dAD criteria have face validity (67), and Rosenberg et al. (72) have demonstrated their clinical application.

SYMPTOMATIC OVERLAP OR ASSESSMENT OVERLAP?

Apathy and depression are frequently associated in AD, due to joint key symptoms of diminished motivation and interest, vegetative symptoms of psychomotor retardation, fatigue and hypersomnia, lack of insight and pessimism, diminished ability to concentrate, and weight loss (9, 11, 60). This symptomatic overlap often results in the misinterpretation of apathy as depression, even in the absence of depressed mood or signs of dysphoria according to the DSM criteria (5, 11, 60, 68, 71). According to the DSM-IV criteria for depression, one main symptom is loss of interest or pleasure in activities, as opposed to depressed mood itself (68). However, in the demented, this loss of interest or pleasure may reflect a loss of motivation or ability, rather than a change in affect or depression (5). This both complicates its assessment (44, 47, 60) and results in apathetic individuals meeting the diagnostic criteria for major depression, even in the absence of dysphoric symptoms (5, 11, 70, 71).

The observed overlap may be explained by methodological variations of assessments relating to symptoms common to both syndromes (e.g., closely related subsets of items, such as diminished interest, psychomotor retardation, lack of energy, loss of insight; or dysphoric items, such as depressed mood, guilt, hopelessness and vegetative symptoms) (2, 11, 70, 79). Research has demonstrated high correlations between apathy and depression scores for items corresponding to symptoms commonly observed in the syndrome of apathy (2, 12, 26, 80), as well as categorization of patients into cohorts of "pure apathy", "pure depression" or "apathy and depression" (3, 10, 45, 81). This has led to the conclusion that apathy and depression have divergent natural histories and can be differentiated (7, 82).

Forsell et al. (83, 84) described depressive symptoms in the elderly as falling into two categories: mood problems (symptoms of dysphoria, feelings of guilt and suicidal ideation) and motivational problems (symptoms of lack of interest, low energy and psychomotor slowing). Depression may be distinguished from apathy (characterized

by lack of emotional responsiveness) according to dysphoric symptoms of sadness, feelings of guilt, self-criticism, helplessness and hopelessness (11, 85-87). The observed loss of interest in depression may rather reflect feelings of despair, pessimism and hopelessness which, combined with dysphoria in depression, differentiate depression from apathy (11, 85). Conversely, apathy is distinguishable from depression according to lack of emotional responsiveness, emotional indifference, 'lack or lessening of ability to initiate in multiple domains (motor, gait, cognitive)' and a lack of concern – not all of which are exclusively observed in depressed individuals (11, 13, 71, p. 16, 86, 87).

Differences are also observed for neuropsychiatric symptoms, apathy being associated with disinhibition and aberrant motor behavior, and depression with anxiety, agitation, irritability and hallucinations (9, 45). The occurrence of negative mood and dysphoric symptoms in depression, but not in apathy, provides a further difference (5). Various studies have demonstrated differences between apathy and depression in AD for associated cognitive deficits (11, 30, 88). Research by Kuzis et al. (30) compared only apathetic, only depressive, and co-morbid apathetic and depressive early AD patients. In contrast with only depressive patients, only apathetic patients showed specific cognitive deficits in naming performance, word list learning, verbal fluency and set-shifting (30). The co-morbid apathetic and depressive group had worse impairments in abstract reasoning ability than those with only apathy, while no association with cognitive dysfunction was found for the only depressive group (11, 30).

Although the concept of apathy as a separate syndrome from depression has received much valid support, there are opposing arguments. First, for Marin (13), the diagnosis of apathy should not be made in the context of diminished levels of consciousness, moderate or severe cognitive deficits, or marked emotional distress, as apathy may be an intrinsic symptom of dementia (21). Although this point is useful in identifying a 'pure' apathy syndrome 'uncontaminated by changes in cognitive or affective domains', conceptual and empirical evidence argues against such an approach (21, p. 1089). One conceptual issue is that a syndrome is defined as a constellation of symptoms without reference to a specific etiology, and it is therefore not clear why apathy should be 'considered a syndrome in some contexts (e.g., stroke) but not in others (e.g., dementia)' (21, p. 1089). A second opposing argument is that some psychopathological syndromes (e.g., apathy and depression) co-occur in some neurodegenerative diseases (21, 26). In response, while the apathetic syndrome is observed most frequently in 'individuals with neurological disorders and some degree of cognitive impairment and depression' (e.g., AD, stroke, or Parkinson's disease) (21, p. 1089, 81, 89), this may be due to the inability of assessments to differentiate between symptoms of apathy, cognitive impairment and depression, as is the case in Parkinson's disease, in which there is an overlap between depression, dementia and apathy (90-92). A third opposing argument is that both DSM-IV and ICD-10 allow for the diagnosis of mild or moderate depression in the absence of depressed mood, while requiring loss of interest or anhedonia ('inability to experience pleasure, as manifested in facial expression, speech, behaviour, lifestyle and the individual's account of personal experience'), or a decrease in energy (21, p. 1090, 93). Starkstein and Leentjens (21, p. 1089) rightly question whether: 1) such a definition adequately explains the high co-occurrence of apathy and depression, 2) such a reliable separation of non-dysphoric depression from apathy may occur, and 3) 'lack of interest and/or anhedonia are core symptoms of diminished motivation', as Starkstein et al.'s (10, 21) apathy diagnostic criteria require diminished goal-directed behavior for apathy (assessed by 'lack of interest'). Accordingly, the above argument for apathy as a symptom of depression must be questioned. On balance, the weight of literary evidence points toward apathy as a separate and distinct syndrome from depression, and this view is further supported by findings on the prevalence of apathy and depression in dementia.

DOES PREVALENCE INDICATE SIMILARITY OR DIFFERENCE?

Prevalence and progression rates further support apathy as a separate syndrome from depression. Apathy is a prominent feature of AD-related behavioral and personality changes (11, 26, 27, 32, 70, 94, 95), appearing early in the course of the disease (reports ranging between 11 and 39% of individuals with MCI) and increasing in prevalence with illness progression until it is universal amongst the severely cognitively impaired (up to 92% of AD patients) (11, 24, 35, 50, 70, 71, 80, 96, 97). Conversely, depression precedes the onset of AD (5, 10, 50, 70, 98, 99) and is often an initial symptom in AD, appearing in mild to moderate stages (including MCI) and becoming less prevalent in more severe stages (46, 56, 100, 101). Prevalence rates of depression (major and minor) in AD reportedly range between 30 and 50% (with more extreme studies reporting rates between 1 and 90%) (44, 46). These inconsistencies may be explained by the large variability in definition, assessment and clinical manifestation in research (44, 46). Notably, as AD progresses, the expression of depressive syndromes changes, resulting in under-recognition of late-life depression due to clinical and nosological ambiguities (83, 102). However, the declining prevalence of depression in more advanced AD stages may be the consequence of assessment difficulties, due to advanced cognitive decline (46, 56).

Apathy also occurs without depression in AD, sug-

gesting that the former is a distinct and distinguishable syndrome from depression (3, 11, 21, 45). Marin et al. (94) demonstrated that 55% of AD patients had high levels of apathy and low levels of depression, whereas 47% of older adults with major depression had low levels of apathy (11). This suggests differential patterns of apathy and depression in AD patients and patients with major depression, 'despite a positive correlation between apathy and depression scores in both groups' (11, p. 1704). These findings of no concomitant depression in AD patients supports apathy as a separate neuropsychiatric syndrome from depression.

Other research demonstrates co-occurrence of apathy and depression varying across neurological conditions, suggesting that these are two neuroanatomically distinct entities (2, 45). Starkstein et al. (26) supported this concept in their longitudinal examination of the association between apathy and depression. Their findings that 25% of non-depressed patients had apathy and that 50% of depressed patients also had apathy led them to conclude that depression is not a requisite for the presence of apathy in AD (26). In addition, they found a significant increase in apathy over time, in that baseline subsyndromal depression was not associated with follow-up apathy levels and baseline apathy levels were a significant predictor of increased follow-up depression (26). This last finding led them to suggest that apathy may be either an early indicator for depression or a prodromal stage of depression (26). However, in the latter case, the prevalence rates of apathy should reflect higher levels of apathy prior to depression. This is not found. While depression is most common in early stages and decreases in prevalence with cognitive decline, apathy increases with increasing cognitive impairment. Therefore, although apathy may be a possible risk factor for the development of later life depression, Starkstein et al.'s (26) proposal of apathy as a prodromal stage of depression requires further investigation. Accordingly, on the basis of current understanding of the prevalence and progression rates of apathy and depression, it is plausible to postulate that apathy and depression are separate syndromes in dementia.

In summary, apathy and depression differ according to prevalence and progression rates. While apathy occurs in early and mild stages of cognitive impairment and increases in prevalence to become universal among the severely cognitively impaired, depression is an initial symptom, already apparent in the pre-clinical stage of MCI and mild to moderate stages of impairment. In contrast to apathy, depression becomes less prevalent with increasing cognitive decline, perhaps as a consequence of methodological limitations (e.g., AD pathology, cognitive decline, and unwillingness or inability to disclose the occurrence of such neuropsychiatric symptoms). The development of more accurate and effective ways of assessing such neuropsychiatric symptoms is required when diagnosis is not predominantly dependent on caregiver reports or clinical interpretations.

A NEUROPATHOLOGICAL EXPLANATION?

Similarities and differences in apathy and depression have not only been found in symptomatic overlaps, but also on a neuropathological level (11). Apathy is most commonly observed in combination with damage to the frontal lobes or subcortical structures connecting them (e.g., frontal lobe lesion) and impairments in these areas are associated particularly with executive dysfunction and cognitive and behavioral changes (11, 38, 71, 103, 104). In particular, apathy is 'correlated with neuronal loss, higher tangle counts and white-matter hyperintensities in areas that are thought to be essential components' of frontal subcortical circuits (11, p. 1701, 105-110). Notably, patients with moderate or severe apathy demonstrate significantly reduced blood flow in the anterior temporal, orbito-frontal, anterior cingulate and dorsolateral prefrontal regions, compared with those with no or mild apathy (31, 50, 111, 112). These findings have resulted in the implication that 'apathy is associated with specific cognitive impairment caused by disruption of these brain areas' (29, p. 2) and, specifically, the involvement of frontal-subcortical circuits originating from frontal cortical regions, which mediate executive function and motivation in apathetic patients (30, 31, 113, 114). Thus, apathy in AD has been closely associated with neuropathological impairments in components of the anterior cingulate frontal-subcortical circuit (e.g., anterior cingulate, nucleus basalis of Meynert, hippocampus, medial frontal region) (5, 105-108).

Conversely, the neuropathology of depression in AD is primarily associated with frontal-striatal and subcortical limbic structures (locus ceruleus, substantia nigra, hippocampus and hypothalamus) (5, 9, 50, 115, 116). *Post-mortem* evidence has demonstrated a reduction in the locus ceruleus cell population, the number of substantia nigra cells, and neurochemical changes, i.e., marked reduction of norepinephrine levels in the middle frontal and temporal cortex cortical regions, increased entorhinal cortex dopamine levels, and normal frontal and temporal cortex serotonin levels – even with significant reduction of serotonin uptake sites in the temporal regions (117-121). *Post-mortem* evidence also suggests selective noradrenergic cell loss in the locus ceruleus and loss of dorsal raphe serotonergic nuclei (56, 119, 122-125). Apoptotic processes occurring as a function of AD may also contribute to the loss of aminergic nuclei, in turn affecting mood (46, 126). Interestingly, the presence of depression correlates with elevated global scores of deep white matter lesions, particularly to frontal lobe white matter (127, 128). However, although findings of functional neuroimaging studies are inconsistent, AD-related depression has been associated with reduced parietal lobe

metabolism, cerebral hypoprofusion in temporal-parietal regions, and hemispheric hypoperfusion in the dorsolateral, frontal, temporal and parietal regions (50).

In summary, while apathy in AD is associated with abnormalities of frontal subcortical circuits (specifically, the 'anterior cingulated which is thought to be responsible for motivated behavior') (29, p. 2), AD-related depression is associated with neuropathology of frontal-striatal and subcortical limbic circuits (e.g., locus ceruleus, substantia nigra, hippocampus, hypothalamus) (9).

Apathy and depression are neuropathologically similar, due to hypoperfusion or hypoactivity in frontal, parietal and temporal regions (5, 9, 11, 108, 111, 115, 116, 129-132). Landes et al. (11, p. 1704) suggested that the 'co-occurrence of apathy and depression may relate to involvement of frontal subcortical circuits in both syndromes'. Other research proposes mixed behavioral presentation of apathy and depression, due to impairment of the frontal circuitry in major depression resulting from the proximity of such subcortical circuits (i.e., a subcortical lesion simultaneously affects multiple circuits) (11, 39, 45, 104, 133, 134). However, while the involvement of frontal subcortical circuits has a long-standing tradition as a heuristic explanation of behavioral problems in neuropsychiatry, this hypothesis may lack heuristic value, as neuropathological differences have been observed in which 'AD patients with isolated motivational or mood disturbances reveal differing cortical dysfunction during early disease, confirming a different neuroanatomical basis for the emergence of apathy and depression in AD' (135, p. 418). Holthoff et al.'s (135) positron emission tomography study showed that apathetic early AD patients had significant glucose metabolism decreases in the left orbitofrontal regions, while hypometabolism in the dorsolateral prefrontal regions was associated with depression.

Other research suggests that apathy and depression differ on a neurochemical basis, apathy being associated with cholinergic deficits and depression with serotoninergic deficits or a dopamine and norepinepherine imbalance (5, 50, 136-138). Symptoms of apathy in early AD are related to cholinergic input loss to the prefrontal and subcortical structures of the nucleus basalis of Meynert, whereas deepening apathy in later stages results from severe cholinergic denervation, and involvement of the prefrontal cortex and the anterior and medial temporal structures supplying adherent input to this circuit (9, 11). Thus, an interaction between neuropathological frontal brain changes and cholinergic deficiency is reflected in AD-related apathy (9).

The identification of more pronounced apathetic symptoms in AD patients exhibiting extra-pyramidal symptoms and empirical results on modulated dopaminergic neurotransmission treatment further suggest that dopamine plays a mediating role in apathetic AD patients (11, 71, 139). Conversely, serotoninergic agents (e.g., selective serotonin re-uptake inhibitors) may worsen apathetic symptoms but relieve depression (45, 86, 140-143). While apathy treatment may be supported by increasing dopaminergic function, serotonergic activity increase is detrimental (33). Thus, cholinomimetic agents reduce apathy but do not affect mood, so that only apathy, and not depression, is relieved by dopaminergic agents (45, 144). One explanation is that depression results from an imbalance in paralimbic neurotransmitter function, whereas apathy may be traced to a functional disconnection of the cortex from the relevant paralimbic input (9). While the treatment of apathy with cholinesterase inhibitors (e.g., tacrine) has demonstrated significant reductions in apathetic symptoms in AD, suggesting a 'cholinergic contribution to the pathophysiology of apathy in AD' (50, p. 852, 145), between 38% (146) and 60% of patients (147) do not respond to this treatment (33). This involvement of differing neurochemical pathways and, to some extent, of neuropathological structures may therefore be a further indication that apathy and depression are two separate syndromes in dementia.

In summary, apathy in AD is associated with bilateral hypoperfusion within the basal ganglia and dorsolateral prefrontal cortex (132), reduction in perfusion of anterior temporal, orbito-frontal, anterior cingulate and dorsolateral prefrontal regions (148, 149), hypometabolism in left orbitofrontal areas (135), and left anterior cingulate neurofibrillary tangle burden (105). Conversely, AD-related depression is associated with hypometabolism in the left prefrontal cortex and superior frontal cortex (135), white matter lesions (127), reduced glucose metabolism in the bilateral anterior cingulate and superior temporal cortex (132) and bilateral superior frontal and left anterior cingulate cortex (131) or parietal lobes (150).

CONCLUSIONS AND FUTURE DIRECTIONS

Although no consensus on the nosological position of apathy in dementia has been reached, apathy, despite some symptomatic overlap with depression, may be viewed as a separate syndrome from depression in dementia. This review provides an overview of the literature focusing on the areas of clinical manifestation, symptomology, assessment, prevalence, and neuropathology. We conclude that, given the evidence, the arguments in support of apathy as a separate syndrome from depression in dementia are persuasive. However, the fact that the definitions of apathy and depression overlap in terms of key symptoms, resulting in a high mis-diagnosis of apathy as depression, raises some concerns. These concerns regard treatment, as medical treatment of depression does not alleviate the negative impact of apathy. To provide sufficient support to individuals suffering from dementia and their caregivers, it is vital that apathy as a syndrome should be recognized and treated. Reaching a

consensus on the definition of apathy within dementia is essential if patients suffering from such neuropsychiatric symptoms are to receive deserved support and attention.

A consensus on the definition of apathy and its nosological position will lead to better development and implementation of diagnostic measures and criteria, more effective research and clinical practice, and better understanding of associated neuropsychiatric disorders in dementia. The identification of apathy as a separate syndrome and its management (whether pharmacologically or non-pharmacologically) requires better understanding of potential risk factors for both apathy and depression in dementia. This is important when considering the direction of future research, specifically on potentially modifiable risk factors for the development of apathy and depression in dementia. While there is ample research on risk factors of AD (151), little research has focused on risk factors for apathy and depression in dementia. Future research should consider the role of behavioral and cognitive models in this context, as these may not only provide further insight and understanding of the multi-dimensionality involved in neuropsychiatric symptoms in dementia, in which depression and/or apathy may not only be characterized as a deficit in motivation or mood, but may also reflect transient modalities to adapt to their environment (152). Future research should also consider the possibility of conversion between apathy and depression, and *vice versa*, as this may provide further understanding of risk factors. Mortby et al. (153) were the first to study midlife motivational abilities as predictors of apathy and depression in dementia, demonstrating that midlife motivational abilities moderate the causal relationship between cognitive impairment and apathy, but not depression. The findings by Mortby et al. (153) – that depression remained stable over time, regardless of severity of impairment, but that apathy increased over time in AD patients – may be interpreted as additional support to the view that apathy and depression are two separate syndromes (11). These findings may provide a new perspective to the ongoing debate on whether behavioral and psychological symptoms of dementia reflect pre-morbid personality traits (e.g., 154-156) preceding apathy and/or depression in dementia. Specifically, these findings may provide stimulation for future research into personality factors or coping styles, to determine whether apathy and/or depression are a state or trait in dementia, as this may provide additional insight into the best approaches for prevention and treatment of both.

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